REMARKS

In the Final Office Action dated March 6, 2003, the Examiner withdrew from consideration claims 26-28 and 31-37 as directed to non-elected species. Applicants respectfully submit that claims 26-28 should be allowable upon allowance of generic claim 21 from which they depend. Applicants reserve the right to file one or more divisional applications claiming the subject matter of claims 31-37, which have been canceled by the amendment submitted herewith.

Upon entry of the present Amendment, claims 21-30 and 38 are pending in the application. Claims 26-28 have been withdrawn from consideration. Claims 31-37 have been canceled. Claims 29 and 38 have been amended to remove exemplary parentheticals and revise the wording of the Markush groups in accordance with standard U.S. claim format. No new matter has been added by this amendment. Applicants submit that the amendment places the claims in condition for allowance. Entry of the amendment is respectfully requested.

Each of the rejections presented in the Final Office Action of March 6, 2003 is addressed individually below.

Rejection of claims 21-22 and 24-25 under 35 U.S.C. § 103(a)

Claims 21-22 and 24-25 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura et al., U.S. Patent No. 6,133,258 ("Shishikura") in view of Csuzdi et al., WO 97/28163 ("Csuzdi"). Applicants respectfully traverse this rejection.

To support a *prima facie* case of obviousness, the cited references must teach or suggest every element of the claimed invention, and must provide a reasonable expectation of success in achieving the claimed invention. MPEP § 2142.

Applicants submit herewith a declaration of one of the inventors, Terence Smith. The declaration presents Dr. Smith's understanding that Applicants' claimed invention would not have been obvious to one of ordinary skill in the art in view of the teachings of the cited prior art references. As explained in the declaration (*see* page 3, paragraph 6), the co-inventors Drs. Smith and Turski were the first to recognize the glutamate ionotropic AMPA receptor as a target for the treatment of demyelinating disorders,

discovering an interaction between the AMPA receptor and paralysis seen in an accepted model of a demyelinating disease. The inventors' work was recognized as an important advance in the field: it was published in Nature Medicine **6**:62-66 (2000) (copy attached), and discussed in the "News and Views" section of Nature Medicine **6**:15-16 (2000) (copy attached). Reflecting this innovation by Drs. Smith and Turski, Applicants' claims 21-22 and 24-25 are directed to methods of treating a demyelinating disorder by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex.

In contrast to Applicants' claims reciting treatment of demyelinating disorders, the cited Shishikura reference discloses certain AMPA receptor antagonists as useful for treating neurodegenerative disease. As recognized in Applicants' specification (*see* page 3, lines 1-4), and discussed in Dr. Smith's declaration (*see* page 2, paragraph 5), it was understood in the art that glutamate played a role in the pathogenesis of certain neurodegenerative conditions, and ionotropic glutamate receptor antagonists were recognized as a therapeutic target for treating neurodegenerative disease. Applicants advanced upon this understanding by establishing a link between neuronal demyelination and glutamate-mediated cell death using accepted animal models of a demyelinating disorder, and by recognizing inhibitors of the interaction of glutamate with the AMPA receptor complex as treatments for demyelinating disorders (*see, e.g.*, specification, page 3, lines 14-24). There is no discussion in Shishikura of the involvement of the AMPA receptor in the treatment of the class of demyelinating disorders, and no teaching or suggestion that an AMPA antagonist could be used to interfere with the process of demyelination. Thus, Shishikura does not disclose or suggest the use of an AMPA receptor inhibitor for treating disorders induced by demyelination. There is no teaching of any link between demyelination and any disease states. Instead, Shishikura simply teaches a narrow class of compounds (neuroprotecting agents) for use in preventing the destruction of neurons.

The Examiner argued that Shishikura teaches a method of treating multiple sclerosis, which is a demyelinating disorder, with an AMPA receptor antagonist. However, the cited disclosure in Shishikura simply provides a laundry list of disorders

that allegedly could be treated using the disclosed compounds. Along with a number of neurodegenerative disorders, the list includes a wide variety of conditions ranging from diabetes to drug dependence to multiple sclerosis (*see, e.g.*, column 2, lines 50-59). There is no teaching or suggestion that the disclosed compounds would be useful for treating demyelination in multiple sclerosis patients, and no enabling disclosure regarding how the disclosed compounds might be used to treat demyelinating disorders. Thus, Shishikura's inclusion of multiple sclerosis in a laundry list of allegedly treatable conditions does not provide sufficient enabling disclosure to teach, suggest, or provide a reasonable expectation of success in achieving Applicants' claimed methods of treating demyelinating disorders using AMPA receptor inhibitors.

As indicated by the Examiner, Csuzdi teaches 2,3-benzodiazepine derivatives and their use as noncompetitive AMPA receptor inhibitors for treating neurological disorders. However, Csuzdi does not discuss demyelinating disorders, and there is no teaching or suggestion that the disclosed 2,3-benzodiazepine derivatives could be used to treat demyelinating disorders. Instead, Csuzdi merely teaches that 2,3-benzodiazepine derivatives can be used to prevent the destruction of neurons.

Thus, as discussed in Dr. Smith's declaration, Shishikura and Csuzdi, alone or in combination, do not teach or suggest the claimed methods of treating demyelinating disorders by administering inhibitors of the interaction of glutamate with the AMPA receptor complex. One of ordinary skill in the art reading Shishikura in combination with Csuzdi would be taught that AMPA receptor inhibitors, such as 2,3-benzodiazepine derivatives, can be used to treat neurodegenerative disorders. However, there is no teaching or suggestion in either reference that AMPA receptor antagonists interfere with the process of demyelination, nor is there any enabling disclosure that would provide one of ordinary skill in the art with a reasonable expectation of success in using AMPA receptor antagonists to treat demyelinating disorders.

Therefore, because Shishikura and Csuzdi do not teach or suggest every limitation of the claimed invention, or provide a reasonable expectation of success in achieving the claimed invention, claims 21-22 and 24-25 are not obvious over the cited

references, alone or in combination. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection under § 103(a).

Rejection of claims 23, 29-30, and 38 under 35 U.S.C. § 103(a)

Claims 23, 29-30, and 38 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura in view of Csuzdi and further in view of Prineas et al., "Demyelinating Diseases," in Greenfield's Neuropathology, 813-896 (1997) ("Prineas"). Applicants respectfully traverse this rejection.

To support a *prima facie* case of obviousness, there must be some suggestion or motivation to combine the teachings of the cited references. The motivation to combine must be found in the prior art, and must not be based on impermissible hindsight in view of Applicants' disclosure. MPEP § 2142.

Applicants' claim 23 is directed to the treatment of certain secondary demyelinating disorders by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex. Claims 29-30 and 38 are directed to methods and compositions for treating a demyelinating disorder by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex in combination with another agent.

As discussed above and in the declaration of Dr. Smith, the combined disclosures of Shishikura and Csuzdi merely teach one of ordinary skill in the art that AMPA receptor inhibitors can be used to treat neurodegenerative disorders. These references do not teach or suggest the treatment of demyelinating diseases generally, or secondary demyelinating disorders in particular.

The Examiner argued that Prineas teaches (i) that interferon-β curtails immune activation by counteracting some of the proinflammatory actions of interferon-γ and reduces the rate of clinical relapses of multiple sclerosis, and (ii) the general pathological features of demyelinating disorders. However, as discussed in Dr. Smith's declaration, Prineas does not disclose or suggest the treatment of demyelinating disorders with inhibitors of the interaction of glutamate with the AMPA receptor complex.

Thus, a *prima facie* case of obviousness has not been established, because the cited references in combination still do not teach or suggest the treatment of demyelinating disorders, and particularly secondary demyelinating disorders, by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex, alone or in combination with another agent. Furthermore, there would be no motivation to combine the teachings of the cited references, because they are directed to distinct subject areas. Specifically, there would be no motivation to combine the teachings of Shishikura and Csuzdi, which relate to agents for treating neurodegenerative diseases, with the teachings of Prineas, which relate to demyelinating diseases. Indeed, the only possible motivation to combine the teachings of Shishikura and Csuzdi disclosing particular AMPA receptor antagonists for treatment of neurodegenerative diseases with the teachings of Prineas regarding demyelinating disorders would be based on improper hindsight in view of Applicants' disclosure.

Thus, claims 23, 29-30, and 38 are not obvious over Shishikura, Csuzdi, and Prineas, alone or in combination, and Applicants respectfully submit that this rejection under § 103(a) should be reconsidered and withdrawn.

Conclusion

In view of the amendment and arguments set forth above and the declaration of Terence Smith submitted herewith, Applicants contend that all of the rejections in the Final Office Action dated March 6, 2003 have been overcome and should be reconsidered and withdrawn. Applicants respectfully submit that all of the pending the claims are in condition for allowance.

Applicants hereby petition for a three-month extension of time pursuant to 37 C.F.R. § 1.136 to respond to the Final Office Action mailed on March 6, 2003. Please deduct the $930.00 fee for this purpose from our Deposit Account No. 08-0219. Please deduct the $320.00 fee for the Notice of Appeal filed herewith from our Deposit Account No. 08-0219 as well. No other fees are believed to be due in association with this submission. However, please charge any other payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is invited to contact the undersigned at the telephone number below in order to expedite prosecution and allowance of this application.

Respectfully submitted,

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